

## **REMARKS**

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following commentary.

### **I. Status of the Claims**

Claims 1-15 and 21-27 were cancelled previously. Claim 17 is cancelled in this response without prejudice or disclaimer thereof. Claim 16 has been amended with exemplary support in the original specification, e.g. in the published application, at page 2, paragraph [0019]; at page 6, paragraph [0076].

Because no new matter is introduced, Applicants respectfully request entry of this amendment. Upon entry, claims 16, 18-20, and 28-32 will be pending.

### **II. Rejection of Claims under 35 U.S.C. §112, second paragraph**

The Examiner rejected claims 16 and 20 for alleged indefiniteness. Applicants respectfully traverse the rejection.

Specifically, the Examiner contends that claim 20 is unclear because base claim 16 is directed to an HSV with an alteration in the  $\gamma$ 34.5 gene, while G207 recited in claim 20 contains mutations in the  $\gamma$ 34.5 gene and the ribonucleotide reductase gene. As the Examiner points out, G207 is known in the art as an HSV having mutations in both  $\gamma$ 34.5 gene and ribonucleotide reductase gene. For greater clarity, claim 20 has been amended to specify that the HSV is G207 expressing the cytokine. Accordingly, the rejection should be withdrawn.

### **III. Rejection of Claims under 35 U.S.C. §112, first paragraph**

The Examiner rejected claims 16-20 and 28-32 for alleged lack of enablement. Claim 17 is cancelled presently. Applicants traverse the rejection as to the remaining claims.

The Examiner is heard to argue that the specification cannot support the range of all alterations to the HSV  $\gamma$ 34.5 gene, including silent mutations. *See* Office Action, section 5, particularly at page 6, the last two paragraphs.

Claim 16 has been amended to specify that the mutation in the  $\gamma$ 34.5 gene results in a lack of function of the  $\gamma$ 34.5 gene product. The revision is amply supported (see the published application, e.g., at page 2, paragraph [0019], and at page 6, paragraph [0076]) and comports with the Examiner's recommendation (Office Action, at page 6, last paragraph). The specification further discloses construction of HSV vectors and impairment of  $\gamma$ 34.5 gene expression (published application, pages 4 and 5). Therefore, the skilled person is enabled by the specification to make HSV mutants as claimed. Accordingly, withdrawal of the rejection is respectfully requested.

#### **IV. Rejection of Claims under 35 U.S.C. §103(a)**

##### **A. Roizman and Vile**

Claims 16, 17, 28 and 29 are rejected over U.S. Patent No. 6,172,047 to Roizman et al. ("Roizman") in view of Vile et al., *Ann. Oncol.* 5 Suppl. 4: 59-65, 1994 ("Vile"). Claim 17 is cancelled. Applicants respectfully traverse the rejection of the remaining claims.

The Examiner's position is that, at the time of filing, one skilled in the art was informed by the alleged teachings of (i) Roizman, that an HSV with mutant  $\gamma$ 34.5 gene could be used as a therapeutic agent, and (ii) Viles, that injection of cells expressing cytokines in animal could diminish tumorigenicity. In light of (i) and (ii), according to the Examiner, it would have been obvious to combine these teachings to arrive at the claimed invention.

Applicants respectfully disagree. To reach his conclusion, the Examiner has applied an "obvious to try" rationale that is improper under the statute and governing case law.

The U.S. Supreme Court's decision, *KSR International Co. v. Teleflex Inc.*, prompted a reconsideration of the obvious-to-try rationale, *i.e.*, positing the obviousness choosing from a finite number of identified, predictable solutions with a reasonable expectation of success. See the EXAMINATION GUIDELINES FOR DETERMINING OBVIOUSNESS UNDER 35 U.S.C. §103..., published in the *Federal Registrar*, Vol. 72, No. 195 (October 10, 2007), hereafter "the Guidelines."

Pursuant to the Guidelines, an examiner seeking to advance an obvious-to-try rationale is obliged to articulate:

- (1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
- (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;
- (3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and
- (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

If any of these findings cannot be made, then this rationale is unavailable to validate a conclusion that the claim(s) in question would have been obvious, within the meaning of Section 103.

In the present instance, the Examiner has failed to meet the initial burden, pursuant to the Guideline requirements, of establishing a *prima facie* case of obviousness. This is so because, contrary to the Examiner's contention, there was no reasonable expectation of success in view of the state of art at the time of filing.

The contemporaneous art was hardly one characterized by "a finite number of identified, predictable potential solutions to the recognized...problem," namely, the treatment of malignant tumors. To the contrary, the skilled artisan would have encountered a panoply of co-treatments

that might be combinable with oncolytic HSV. As demonstrated by the declaration of inventor Samuel Rabkin (previously submitted in copending application Serial No. 10/748,233, a copy of which is appended herewith), moreover, the relevant pre-filing literature was replete with articles evidencing a contemporaneous understanding in the field that cytokines, such as IL-1 $\alpha$ , IL-2, IL-3, TNF, IFN- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$ , M-CSF-1 and GM-CSF, **protect** a host from HSV infection and **diminish** replication of HSV in the host cells.\*

As Dr. Rabkin attests, this conventional wisdom of the day would have led the skilled artisan away from expressing cytokines in the replication competent HSV for purposes of tumor therapy, as presently claimed, since therapy with such mutant HSV requires HSV to infect and replicate in tumor cells of the host, in order to kill tumor cells. *See* published application, at page 2, paragraph [0012]. The further alteration of such mutant HSV to express cytokines is done to elicit an immune response against the tumor cell, enhanced by cell killing due to the HSV infection. *Id.* At page 6, paragraph [0076]. Yet, the skilled artisan would have expected that expression of a cytokine to protect the cells from HSV infection and replication, which would diminish the therapeutic effect of the claimed, replication-competent HSV. By the same token, the skilled artisan would not have expected, as the Examiner contends, that combining cytokines with the mutant HSV might result in an enhanced tumor therapy.

The Examiner has advanced no contravening evidence or compelling logic to support the proposition that the skilled artisan would have been motivated to express the cytokines in the mutant HSV. In fact, such a combination runs counter the conventional wisdom at the time of filing. Accordingly, the claimed invention is non-obvious over the cited art, and the subject rejection should be withdrawn.

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\* Here “infection” is given its common usage, connoting “invasion by and multiplication of pathogenic microorganisms in a bodily part or tissue, which may produce subsequent tissue injury and progress to overt disease through a variety of cellular or toxic mechanisms.” THE AMERICAN HERITAGE® DICTIONARY OF THE ENGLISH LANGUAGE, 4<sup>th</sup> ed. (Houghton Mifflin Company, 2004), submitted herewith as Exhibit 1.

**B. Roizman, Vile and Chang**

The Examiner rejected claims 16 and 18-19 for alleged obviousness over Roizman in view of Vile and further in view of Chang et al., *Virology* 185: 437-440, 1991 (“Chang”). Applicants respectfully traverse the rejection.

The teachings of Roizman and Vile, as well as the patentability of claim 16, are discussed *supra*. Claims 18-19 are dependent from a non-obvious base claim 16, and therefore are non-obvious.

**C. Roizman, Vile, McKay and Wright**

The Examiner rejected claims 30-32 for alleged obviousness over Roizman taken with Chang, and further in view of PCT publication No. WO 92/14821 by McKay *et al.* (“McKay”) and U.S. Patent No. 5,639,656 to Wright, Jr. (“Wright”). Applicants respectfully traverse the rejection.

Each of claims 30-32 ultimately depends from claim 16. Since, as discussed above, claim 16 is non-obvious over the cited art, it follows that claims 30-32 likewise are patentable of that art. Applicants respectfully request withdrawal of the rejection, therefore.

**CONCLUSION**

Applicants submit that this application is in condition for allowance, and they request and early indication to this effect. Examiner Shen is invited to contact the undersigned directly, should he believe that any issue warrants further consideration.

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 CFR §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account.

If any extension is needed for timely acceptance of submitted papers, Applicants hereby petition for such extension under 37 CFR § 1.136 and authorize payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

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